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EXAMINER	
ROYDS, LESLIE A	
ART UNIT	**PAPER NUMBER**
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	**Application No.** 10/677,752	**Applicant(s)** STAMLER, JONATHAN S.	
	Examiner Leslie A. Royds	**Art Unit** 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *1-32 and 38-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/2/04 & 2/11/05*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

DETAILED ACTION

Claims 1-44 are presented for examination.

Acknowledgement is made of the present application as a continuation-in-part (CIP) application of U.S. Patent Application No. 10/608,120, filed June 30, 2003, which is a continuation of U.S. Patent Application No. 10/280,085, filed October 25, 2002, now issued as U.S. Patent No. 6,627,602, which is a CIP application of U.S. Patent Application No. 09/986,807, filed November 13, 2001, now issued as U.S. Patent No. 6,472,390. Applicant's Information Disclosure Statements (IDS) filed January 2, 2004 (one page) and February 11, 2005 (one page) have each been received and entered into the application. As reflected by the attached, completed copy of form PTO-1449 (two pages total), the Examiner has considered the cited references, except the Nozik-Grayck et al. reference denoted as "C1" on the IDS filed February 11, 2005. Applicant's response filed January 19, 2006 to the requirement for restriction/election dated December 6, 2005 has also been received and entered into the application.

Requirement for Restriction/Election

Applicant's election of the invention of Group II (claims 33-37), drawn to a method for the prophylaxis or treatment of a patient with a neurodegenerative disease associated with a receptor having a cysteine residue or other cysteine containing protein that is modified by a thiol reactive agent comprising the administration of said thiol reactive agent, in the reply filed January 19, 2006, is acknowledged. In the absence of any remarks or evidence to the contrary, the election is herein treated as an election **without traverse**.

Therefore, for the reasons above and those made of record at pages 2-5 of the previous Office Action dated December 6, 2005, the restriction requirement is deemed proper and is made **FINAL**.

Claims 1-32 and 38-44 are **withdrawn** from further consideration pursuant to 37 C.F.R. 1.142(b), as being drawn to non-elected species.

The claims corresponding to the elected subject matter are claims 33-37 and such claims are herein acted on the merits.

Applicant's Claim for Priority under 35 U.S.C. 120

Applicant's claim for the benefit of three prior-filed applications under 35 U.S.C. §120 is acknowledged. Applicant is reminded that the later-filed application must be an application for patent for an invention that has been disclosed in the parent applications. The disclosure of the invention in the parent applications and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Applicant has failed to comply with the conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §120 because the subject matter disclosed in U.S. Patent Application No. 09/986,807, filed November 13, 2001; U.S. Patent Application No. 10/280,085, filed October 25, 2002; or U.S. Patent Application No. 10/608,120, filed June 30, 2003, does not contain sufficient support and enablement as required under 35 U.S.C. 112, first paragraph, for the presently claimed subject matter. Specifically, the disclosure of the application to which the present application claims priority does not reasonably disclose or suggest a thiol reactive agent for the treatment of a neurodegenerative disease associated with a receptor having a cysteine residue or other cysteine containing protein that is modified by a thiol reactive agent to inhibit its function. Accordingly, Applicant's claim for priority to U.S. Patent Application No. 09/986,807; U.S. Patent Application No. 10/280,085; or U.S. Patent Application No. 10/608,120 is, respectfully, denied. Claims 33-37 are properly granted the effective filing date of the filing date of the present application (October 3, 2003).

Claim Rejections - 35 USC § 112, First Paragraph, Written Description and Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description Requirement

Claims 33-37 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. The claim contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

An Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams and formula that fully set forth the claimed invention. See *Lockwood v. American Airlines, Inc.*, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

In particular, the specification as originally filed fails to provide sufficient written description of any agent or compound, other than the exemplary agents disclosed at the paragraph bridging pages 11 to 12 and the exemplary nitric oxide or nitric oxide donor compounds disclosed at paragraph 3 of page 16 of the present disclosure, such as those NO donors disclosed in U.S. Patent No. 6,472,390 and, preferably, ethyl nitrite, S-nitrosoglutathione, nitrosoallopurinol or Angeli's salt, that is a thiol reactive agent (see present claim 33), nor does it provide adequate written description of a representative number of species, and further how such species would have been representative of the activity of the class of agents as a whole, that is required to claim all of the possible thiol reactive agents that would have utility in the presently claimed method. In addition, the specification as originally filed also fails to provide sufficient written description of what neurodegenerative diseases, other than the exemplary diseases Huntington's disease, Alzheimer's disease, Parkinson's disease or amyotrophic lateral sclerosis, that are associated with a receptor having a cysteine residue or other cysteine containing protein that is modified by a thiol reactive agent to inhibit its function.

Applicant has failed to provide sufficient evidence demonstrating that they were in possession of all known thiol reactive agents for the treatment of all known neurodegenerative diseases associated with a receptor having a cysteine residue or other cysteine containing protein that is modified by a thiol reactive agent to inhibit its function. While methods of screening or selecting agents for such a function would have been plainly obvious to one of ordinary skill in the art, particularly in view of the methods disclosed herein the present specification, such is not sufficient disclosure to identify the particular compound(s) or group(s) of compounds that may have been reasonably expected or known to have exhibited such a function and, thus, would have had utility in the presently claimed method. Furthermore, while methods of determining what neurodegenerative diseases may be associated with a cysteine residue or other cysteine containing protein may also have been obvious to one of ordinary skill in the art, such is not sufficient disclosure to identify those particular diseases that may have been related to a cysteine residue or a cysteine containing protein and, thus, would have been improved with the administration of a thiol reactive agent.

First, Applicant has failed to disclose any relevant, identifying characteristics, such as structure or other physical or chemical properties, or other functional characteristics, beyond the mere disclosure of the generic action of being a "thiol reactive agent" that would have been sufficient to show that Applicant was in possession of the claimed genus of such agents. See *Eli Lilly,* 119F.3d at 1568, 43 USPQ2d at 1406. See also MPEP §2163.

Applicant's attention is directed to the MPEP at §2163, which states, "The issue of a lack of adequate written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the Applicant had possession of the claimed invention."

In support of the present claims to the use of thiol reactive agents, Applicant states in the present specification as originally filed, "The thiol reactive treating agents for the fifth embodiment include not only the thiol reactive agents of the first embodiment, but also additionally nitric oxide and related redox species and oxidation states and oxidized derivative thereof as well as NO donors. NO donors for use in the fifth embodiment include those listed in U.S. Patent No. 6,472,390, the whole of which is included herein by reference. Preferred NO donors for use in the fifth embodiment include ethyl nitrite, S-nitrosoglutathione, nitrosoallopurinol and Angeli's salt. The thiol reactive agent is selected by the method of selecting set forth in the first embodiment." (see page 16, second full paragraph) The thiol reactive agents of the first embodiment are defined at page 11, which states, "Thiol reactive agents for use in the first embodiment herein, include, for example, avicins, arsenicals...In one variation of the invention, penicillin and/or hydrogen sulfide are excluded as a treating agent."

However, the disclosure of these agents is merely exemplary. Applicant has failed to provide any limiting definition of a structure of other physical or chemical properties, or other functional characteristics, that would readily identify to one of ordinary skill in the art what genus of compounds is actually intended by this statement of function alone, what compounds within such a genus were intended to be within the scope of the presently claimed method and whether such a genus was actually within the possession of Applicant at the time of the invention. Applicant is again directed to the MPEP at §2163, which states, "An Applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that Applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. See *Enzo Biochem*, 323 F.3d at 964, 63 USPQ2d at 1613."

It is noted again that Applicant has failed to define the presently claimed genus of compounds in such a manner sufficient to support the claim the Applicant was in possession of the use of the entirety of such a genus of compounds at the time of the invention. To claim a genus of agents that is capable of performing a certain function requires more than just a definition of its function. Such agents must be specifically described by a formula, function, activity and physical characteristics and cannot simply be a prophetic claim to agents with that function that may exist in the art, but have not yet been identified. "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.,* 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004).

Thus, the mere fact that Applicant may have found that the use of a compound known to possess such a thiol reactive function as that presently claimed is not sufficient to claim the entire genus of compounds that has not yet been identified or described in such a way as to demonstrate to one of ordinary skill in the art that such compounds existed, had already been discovered as a distinct and limited class of compounds and were known at the time of the invention such that the use of such compounds in a method of treating neurodegenerative diseases associated with a receptor having a cysteine residue or other cysteine containing protein was well within the possession of Applicant. However, in the absence of sufficient disclosure or description identifying the compounds intended to comprise the class of compounds intended to be within the scope of the present invention, were the skilled artisan to attempt to determine what other agents were included in the genus of compounds that were considered thiol reactive agents, such a person would not be able to rely upon the description provided by Applicant in the present disclosure.

Considering the teachings provided in the specification as originally filed, Applicant has failed to provide the necessary teachings, by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figured, diagrams and formula that fully set forth the claimed invention, in such a way as to reasonably convey to one skilled in the relevant art that Applicant had possession of the entire genus of compounds considered to be thiol reactive agents as recited in present claim 33.

Substantially the same reasoning applies to Applicant's present claim to the treatment of "neurodegenerative diseases associated with a receptor having a cysteine residue or other cysteine containing protein that is modified by a thiol reactive agent to inhibit its function". Applicant has failed to disclose any relevant, identifying characteristics, other than the generic association of the disease to a receptor containing a cysteine residue or other cysteine containing protein, which would have been sufficient to show that Applicant was in possession of the claimed genus of such diseases.

In support of the present claim to "neurodegenerative diseases associated with a receptor having a cysteine residue or other cysteine containing protein that is modified by a thiol reactive agent to inhibit its function", Applicant states in the present specification as originally filed, "The neurodegenerative diseases associated with a protein having a cysteine residue for the fifth embodiment herein, include, for example, Huntington's disease, Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis." (see page 16, first full paragraph)

However, once again, the disclosure of such neurodegenerative diseases is merely exemplary. Applicant has failed to provide any limiting definition or particular characteristics that would readily identify to one of ordinary skill in the art what genus of neurodegenerative diseases is intended by this statement of generic association alone and whether such a genus of diseases was actually within the possession of Applicant at the time of the invention.

It is reiterated that Applicant has failed to define the presently claimed genus of neurodegenerative diseases in such a manner sufficient to support the claim that Applicant was in possession of the treatment of such a genus of diseases at the time of the invention. To claim such a genus requires more than just a general association with a potentially dysfunctional protein residue. Such a genus must be sufficiently described by particular characteristics that distinctly limit the genus to the particular group that Applicant has patentably discovered and cannot simply be a prophetic claim to other diseases that may have the same association with a dysfunctional protein residue and also exist in the art, but have not yet been identified.

Thus, the mere fact that Applicant may have found that a neurodegenerative disease may be associated with a particular receptor having a cysteine residue or other cysteine containing protein is not sufficient to claim a genus of diseases that has not yet been identified or described in such a way as to demonstrate to one of ordinary skill in the art that such diseases existed, had already been discovered as a distinct class of disorders and were known at the time of the invention such that the use of such presently claimed "thiol reactive agents" for the treatment of such diseases was well within the possession of Applicant. In the absence of sufficient disclosure or description identifying those diseases intended to be within the scope of the present invention, were the skilled artisan to attempt to determine what other neurodegenerative diseases were included in the genus of neurodegenerative diseases associated with a receptor having a cysteine residue or other cysteine containing protein, such a person would not be able to rely upon the description provided by Applicant in the present disclosure.

Considering the teachings in the specification as originally filed, Applicant has failed to provide the necessary teachings, by describing the claimed invention with all of its limitations using such descriptive means that fully set forth the claimed invention, in such a way as to reasonably convey to one skilled in the relevant art that Applicant had possession of the genus of neurodegenerative diseases associated with a receptor having a cysteine reside or other cysteine containing protein as recited in present claim 33.

For these reasons, the claims are considered to lack sufficient written description and are properly rejected under 35 U.S.C. 112, first paragraph.

Scope of Enablement Requirement

Claims 33-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of (1) Alzheimer's disease; (2) Huntington's disease; (3) Parkinson's disease; or (4) amyotrophic lateral sclerosis using selenite or 4,4'-dipyridyldisulfide; S-nitrosoglutathione or 4,4'-dipyridyldisulfide; Angeli's salt; or isosorbide dinitrate or memantine-N-ethyl-maleimide, respectively, does not reasonably provide enablement for the prevention or treatment of ***any*** neurodegenerative disease associated with a receptor having a cysteine residue or other cysteine containing protein that is modified by a thiol reactive agent using ***any*** thiol reactive agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;

3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

It is noted that Applicant has provided a non-limiting description of those neurodegenerative diseases that are intended to be within the scope of the invention, including, for example, Huntington's disease, Alzheimer's disease, Parkinson's disease or amyotrophic lateral sclerosis (first full paragraph at page 16). For the purposes of consideration under 35 U.S.C. 112, first paragraph, insofar as the present claims read upon prophylaxis, the Examiner has focused in the specific condition of Alzheimer's disease. However, the reasons stated here concerning the burden of enabling the prophylaxis of Alzheimer's disease apply also to the other above-mentioned conditions, but for the obvious different in the type of disorder.

Factors 1 and 2) The present invention is drawn to a method for the prophylaxis or treatment of a patient with a neurodegenerative disease associated with a receptor, such as a nerve cell or a cysteine protease, having a cysteine residue or other cysteine containing protein that is modified by a thiol reactive agent to inhibit its function, or at risk therefor, comprising administering to said patient a therapeutically effective amount of said thiol reactive agent, provided that when the thiol reactive agent is NO or an NO donor, the NO or NO donor is administered in an amount which provides a submicromolar concentration of NO or NO donor in the patient's blood. The thiol reactive agent may be either NO, an NO donor that donates nitric oxide or a related redox species and provides bioactivity that is identified with nitric oxide, or it may be an agent other than an NO donor.

Factors 3 and 7) Insofar as the claims read upon prophylaxis of neurodegenerative diseases, e.g., Alzheimer's disease, one skilled in the art could not practice the presently claimed subject matter without undue experimentation because the artisan would not accept on its face that patients at risk for a neurodegenerative disease, such as, for example, Alzheimer's disease, could be effectively identified and treated with the claimed active agent(s) prior to the development of such a condition, since such a situation would essentially amount to the prevention of such a condition, since it had not yet developed in the subject. Based on the state of the art, as discussed below, the artisan would have only accepted that the symptoms and conditions outwardly exhibited by a person afflicted with Alzheimer's disease could be ameliorated, rather than that the disease itself could actually be prevented.

As set forth in *In re Marzocchi et al.*, 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains teaching of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112 *unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support*; assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or se will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling." (emphasis added)

The term "prophylaxis" in the present claims is a term that, interpreted in its broadest sense in accordance with the MPEP at §2111, circumscribes a method of absolute success insofar as it would require the identification of patients at risk for a neurodegenerative condition and treating them with the presently claimed agent(s) to prevent them from ever developing such a condition. In other words, the process of identifying patients at risk prior to developing the disorder would essentially amount to the prevention of such a disorder in those patients. That is, in order to be enabled to practice the present invention, the skilled artisan would have to accept that by administering the presently claimed combination of active agents, the development of Alzheimer's disease would be prevented and that there would be a reasonable guarantee that Alzheimer's disease would never progress. Such a situation is sufficiently unusual that data would need to be shown in order to establish that Alzheimer's disease could be kept from ever developing simply by administering the claimed active agent. Because absolute success is not reasonably possible with most diseases or disorders, especially a condition as complex and poorly understood as Alzheimer's disease, the specification, which lacks an objective showing that such a disease could be prevented in such a manner, is viewed as lacking an enabling disclosure of the same.

Here, the objective truth of the statement that Alzheimer's disease may be prevented is doubted. Alzheimer's disease is particularly elusive and manifests itself in a variety of different ways in different subjects such that one cannot be entirely sure that the disease is truly the cause of the signs and symptoms of disorder exhibited by the patient. A diagnosis of Alzheimer's disease is tentative, at best, until confirmation of the diagnosis can be confirmed by the presence of amyloid deposits in the brain at autopsy (see Cecil's Textbook of Medicine, "Differential Diagnosis", page 2043 at column 1).

Such difficulties in diagnosis are recognized in the art. Applicant's attention is drawn to Cecil's Textbook of Medicine, which states, "In a patient with clinical findings suggesting Alzheimer's disease, other causes of dementia should be excluded by history, examination, and the laboratory studies described above. CSF evaluation for amyloid protein and tau protein can increase the likelihood of a diagnosis of Alzheimer's disease, but they are not sufficiently specific to be of routine value in screening or early diagnosis of Alzheimer's disease...Presence of the apoE4 allele makes it very likely that the patient's dementia is produced by Alzheimer's disease. ApoE testing does not have predictive value for asymptomatic individuals." (see Cecil's Textbook of Medicine, "Diagnosis", column 2 at page 2044)

In this regard, it is also noted that the art acknowledges only certain criteria for definitive diagnosis of Alzheimer's disease, see in particular Gauthier et al., (Can. Med. Assoc. J, Oct 15, 1997, 157(8): 1047-52), Greicius et al. (J Neurol. Neurosurg. Psychiatry, 2002 Jun; 72(6):691-700) and Gasparini et al. (FASEB J., 12, Jan. 1998, pp. 17-34). Post mortem analysis of brain tissue for the characteristics of amyloid plaques is considered necessary for a definitive diagnosis. This is because the art has come to recognize its presence in essentially all cases. However, to achieve diagnostic status took years of evaluative procedures, both pre- and post-mortem, confirming that every case had a degree of this pathology. Even so, diagnostic application is often problematic given variable peptide expression patterns among clinically similar and dissimilar diseases states (see Greicius et al.).

Given that there a only a few factors that are recognized to have moderate, if any, predictive value in determining the likelihood that patients develop such a disease or to even determine whether patients actually have such a disease, since many of the early signs of Alzheimer's disease are common complaints of aging or result from other neurological conditions, such as depression, where memory impairment is not present (see Cecil's Textbook of Medicine, "Evaluation of Dementia", column 1, page 2042), one of ordinary skill in the art would not accept on its face Applicant's statement that Alzheimer's disease could be prevented using the presently claimed active agents. Not only is the population in need of such treatment not well defined in the art because of the difficulties associated with making an accurate diagnosis, but the disease is also sufficiently complicated and poorly understood such that the idea that any active agent (including that presently claimed) would be capable of preventing such a condition via administration of the presently claimed agent(s) would not have been reasonably expected by the skilled artisan. The artisan would have required sufficient direction as to how the administration of the presently claimed active agent(s) could actually determine the population of patients in need of prevention and how the presently claimed agent(s) could treat the development of Alzheimer's disease such that the artisan would have been imbued with at least a reasonable expectation of success. Such success would not have been reasonably expected given that the concept of a single agent, or even a combination of agents, that is effective against the development of Alzheimer's disease would have been unique and, thus, met with a great deal of skepticism.

In addition, Applicant has stated on the record that, "Moreover, it has been discovered herein that there are multiple different classes of thiol in proteins characterized by different reactivities to a reagent and that different thiols that have a common reactivity to a thiol reactive agent, when modified, elicit different effects...It cannot be predicted that if a particular effect is obtained with some thiol reactive agent, that the same effect will be obtained with a different thiol reactive agents." (see paragraph bridging pages 3-4) Such is a clear teaching that there was significant unpredictability in the art such that the results shown with one agent would not have been reasonably suggestive of achieving the same results using another thiol reactive agent. In light of such unpredictability, the disclosure necessary to enable the present invention is much greater because Applicant must provide reasonable or scientifically sound rationale as to how the data demonstrated in the present specification with those six exemplified agents can be extrapolated to the larger genus of "thiol reactive agents" in general, since he has admitted on the record that one *cannot* reasonably expect the same activity from different agents because each agent is so disparate in nature and activity.

Factor 4) Applicant has merely disclosed that by administering any of the claimed active agents in a patient at risk for Alzheimer's disease, one may treat such a condition in a patient. Based on the discussion in Section 3 above, however, such disclosure clearly is not adequate direction or guidance as to how the proposed active agent(s) could be employed to accomplish the treatment of Alzheimer's disease, or any one of the other neurodegenerative diseases, in a predictable manner.

Furthermore, Applicant has also merely disclosed the genus of "thiol reactive agents" and that by administering one of such a genus of compounds in a patient with a neurodegenerative disease associated with a receptor having a cysteine residue or cysteine containing protein that can be modified by such an agent, one may treat such a condition in a patient. However, based on the discussion above under the heading "Written Description", Applicant has not adequately identified what compounds aside from those exemplary compounds in the present specification, fall within the genus of "thiol reactive agents". In addition, Applicant has failed to demonstrate that he was in possession of the whole genus of compounds that fell within such a functional recitation. Furthermore, the mere exemplification of six such agents is not sufficient to claim an entire genus of compounds without so much as even identifying the other compounds that fall within such a genus and would have had utility in the present invention and also how it would have been reasonable or scientifically sound to extrapolate the results shown with any one of the six agents exemplified in the specification (see Examples XXVII, XXVIII, XXXIII and XXXIV) to be representative of the activity of any one such agent falling within such genus, particularly in light of the fact that the activity demonstrated by the agents is highly variable and does not exhibit any distinct or suggested pattern. Such disclosure, or lack thereof, clearly is not adequate direction or guidance as to how the proposed active agent(s) could be employed to accomplish the treatment of a neurodegenerative disease associated with a receptor having a cysteine residue or other cysteine containing protein in a predictable manner.

Moreover, the same reasoning applies to the genus of "neurodegenerative diseases associated with a receptor having a cysteine residue or other cysteine containing protein that is modified by a thiol reactive agent." Although Applicant has exemplified four diseases within such a genus, the specification fails to define what diseases other than those exemplary diseases fall within such a genus as presently claimed. In addition, Applicant has failed to describe any reasonable or scientifically sound rationale as to why those four diseases exemplified in the specification would have been representative of any neurodegenerative disease known to have the same association. In other words, the specification is clearly lacking in adequate direction or guidance in this respect as well.

Factor 5) The specification merely discloses that use of the presently claimed agent(s) has activity in the prevention of Alzheimer's disease. Although Applicant discloses that prevention may be achieved, the instant specification does not provide guidance as to how one skilled in the art would accomplish such an objective of preventing Alzheimer's disease or any one other neurodegenerative diseases since it cannot be reasonably guaranteed, in light of what was known in the art at the time of the invention, that such a condition could be prevented. Nor is there any guidance provided as to a specific protocol to be utilized in order to show the efficacy of the presently claimed active agent for the treatment of such a condition.

The specification is also lacking guidance as to how one skilled in the art would accomplish the therapeutic objective of treating a neurodegenerative disease associated with a receptor having a cysteine residue or other cysteine containing protein that may be modified by the presently claimed active agent because Applicant has not reasonably described such a genus of "thiol reactive agents" or "neurodegenerative diseases..." in such a way as to indicate that Applicant was actually in possession of such a genus of agents or such a genus of diseases at the time of the invention and, further, how such agents or diseases that fall within such a genus could have been accurately identified.

The Examiner acknowledges that the Office does not require the presence of working examples to be present in the disclosure of the invention (see MPEP §2164.02). However, Applicant has only provided four examples (see Examples XXVII, XXVIII, XXXIII and XXXIV) of the use of selenite and 4,4'-dipyridyldisulfide for Alzheimer's disease; S-nitrosoglutathione and 4,4'-dipyridyldisulfide for Huntington's disease; Angeli's salt for Parkinson's disease; and isosorbide dinitrate and memantine-N-ethyl-maleimide for amyotrophic lateral sclerosis. In the absence of sufficient disclosure as to what other agents or diseases are included the genus of "thiol reactive agents" or "neurodegenerative diseases associated with a receptor having a cysteine residue or other cysteine containing protein" and how such agents or diseases could actually be identified, and further in the absence of any sound scientific reasoning as to why the therapeutic effect noted in the Examples (see XXVII, XXVIII, XXXIII and XXXIV) would have been reasonably representative of the activity of any other thiol reactive agent in treating such a disease(s), it remains that the Office would require appropriate disclosure to show that Applicant had a reasonable basis to support the contention that the use of any one agent failing within such a genus of agents would have activity in the treatment of any one disease falling within such a genus of diseases, since the present specification fails to enable one of ordinary skill in the art to practice the entire scope of the presently claimed invention.

Factor 6) The burden of enabling the prevention of Alzheimer's disease is much greater that simply enabling, for example, the improvement of the individual symptoms resulting from such a condition. Furthermore, the burden of enabling the entire scope of all known thiol reactive agents for the treatment of neurodegenerative diseases associated with a receptor containing a cysteine residue or other cysteine containing protein is also much greater than simply enabling the treatment of a particular disease with a particular agent, such as those combinations defined in Example XXVII, XXVIII, XXXIII and XXXIV. Since the present specification would not enable the skilled artisan to practice prevention of neurodegenerative diseases or to identify the agents that fall within the genus "thiol reactive agents" or the diseases that fall within the genus "neurodegenerative diseases associated with a receptor containing a cysteine residue or other cysteine containing protein", nor would it enable the skilled artisan to treat any one such disease falling with such a genus with any one such agent falling within such a genus, a clear burden of undue experimentation would be placed upon the skilled artisan in order to practice these aspects of the invention.

Factor 8) In view of the discussion of each of the preceding seven factors, the level of skill in this art is high and is at least that of a medical doctor with several years of experience in the art.

Summary

As the cited art and discussion of the above 8 factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that the presently claimed therapeutic objective could actually be achieved in light of the present disclosure. In other words, in order to actually achieve the therapeutic objective of the present claims, it is clear from the discussion above that the skilled artisan could not rely on Applicant's disclosure as required by 35 U.S.C. §112, first paragraph. Given that the art fails to recognize such a genus of compounds or such a genus of diseases and Applicant has failed to provide sufficient description of such a genus to demonstrate that he was in possession of the full scope of what is presently claimed, the skilled artisan would be faced with the impermissible burden of undue experimentation in order to practice the presently claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

I Claims 33-34 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Lipton (U.S. Patent No. 5,234,956; 1993) in light of Lemere et al. ("The Lysosomal Cysteine Protease, Cathepsin S, Is Increased in Alzheimer's Disease and Down Syndrome Brain", *American Journal of Pathology*, 1995) and Stedman's Medical Dictionary (1972), both cited to show facts.

In accordance with the MPEP at §2131.01, it is proper to rely upon a secondary reference for a rejection made under 35 U.S.C. 102, provided that the secondary reference is relied upon to show that a characteristic not disclosed by the primary reference is inherent.

Lipton teaches a method of reducing NMDA receptor complex-mediated neuronal damage (col.1, lines 49-53; see present claim 37), such as the disorder Alzheimer's disease (col.2, lines 27-34; see present claims 33 and 36), by administering a nitric-oxide generating compound (col.1, lines 49-53; see present claims 33-34), such as nitroglycerin (col.2, lines 22-26), nitroprusside (col.2, lines 22-26), isosorbide mononitrate (col.6, lines 16-27) or isosorbide dinitrate (col.6, lines 16-27), in a concentration effective to cause such a reduction, such as 0.01-1000 mg/day in divided doses (col.6, lines 16-27; see present claim 33).

Lamere et al. ("The Lysosomal Cysteine Protease, Cathepsin S, Is Increased in Alzheimer's Disease and Down Syndrome Brain", *American Journal of Pathology*, 1995) is relied upon to show that the neurological disease Alzheimer's disease was known in the art to be associated with an increase in the lysosomal cysteine protease, cathepsin S (see abstract and "Discussion" at pages 855-858). Thus, though Lipton does not expressly acknowledge that Alzheimer's disease is a neurodegenerative disease associated with a cysteine protease, such was necessarily known to be the case at the time of the invention and is considered to be a characteristic inherent to the disease.

Stedman's Medical Dictionary has been relied upon to show that the neuronal damage is synonymous with nerve damage, because neuron is synonymous with nerve cell (see pages 835-836 and 846). Thus, the fact that Lipton teaches neuronal damage resulting from stimulation of the NMDA receptor-channel complex by homocysteic acid, cysteine sulphinic acid or cysteic acid (see col.2, line 63-col.3, line 3), such is considered to meet Applicant's limitation of claims 33 and 37, wherein the neurodegenerative disease is associated with a nerve cell having a cysteine residue or other cysteine containing protein (i.e., considered to be met by the teaching of homocysteic acid, cysteine sulphinic acid or cysteic acid).

It is noted that the limitation "where the treatment would affect an allosteric cysteine but not other cysteine" as recited in present claim 36 has been considered, but fails to impart any patentable distinction to the present invention over that disclosed by the prior art. Such a limitation amounts to no more than a recitation of the end result of the active agent after it has already been administered to the patient. Because the same agent is being administered for the same disease to the same host as presently claimed, any function that the active agent may have after administration is considered to be the necessary end result of the treatment. Thus, absent any factual evidence to the contrary, such a limitation is considered to necessarily occur in the disclosure of Lipton and is properly anticipated by the reference.

Lastly, it is further noted that Applicant has failed to define the threshold concentration in which the NO or NO donor must be present in order to meet the limitation that a "submicromolar concentration of NO or NO donor" is provided in the patient's blood. Thus, there is no reason to doubt that Lipton's teaching of the administration of 0.01-1000 mg/day (col.6, lines 16-27) of a nitric-oxide generating compound would not generate a submicromolar concentration of active agent in the patient's blood, absent any factual evidence to the contrary.

II Claims 33 and 35-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Duncan (WO 02/020022; March 2002) in light of Lemere et al. ("The Lysosomal Cysteine Protease, Cathepsin S, Is Increased in Alzheimer's Disease and Down Syndrome Brain", *American Journal of Pathology*, 1995), cited to show a fact.

In accordance with the MPEP at §2131.01, it is proper to rely upon a secondary reference for a rejection made under 35 U.S.C. 102, provided that the secondary reference is relied upon to show that a characteristic not disclosed by the primary reference is inherent.

Duncan teaches a method for treating neurologic disorders, such as Alzheimer's disease (page 2, lines 18-21; see present claim 33 and 36), by administering an effective amount of a tetracycline compound, such as those defined by formula (I) (considered to meet Applicant's limitation of "wherein the thiol reactive agent is not an NO donor" as recited in present claim 35; page 2 lines 18-21 and page 2, line 25-page 3, line 6).

Lamere et al. ("The Lysosomal Cysteine Protease, Cathepsin S, Is Increased in Alzheimer's Disease and Down Syndrome Brain", *American Journal of Pathology*, 1995) is relied upon to show that the neurological disease Alzheimer's disease was known in the art to be associated with an increase in the lysosomal cysteine protease, cathepsin S (see abstract and "Discussion" at pages 855-858). Thus, though Duncan does not expressly acknowledge that Alzheimer's disease is a neurodegenerative disease associated with a cysteine protease, such was necessarily known to be the case at the time of the invention and is considered to be a characteristic inherent to the disease.

It is noted that the limitation "where the treatment would affect an allosteric cysteine but not other cysteine" as recited in present claim 36 has been considered, but fails to impart any patentable distinction to the present invention over that disclosed by the prior art. Such a limitation amounts to no more than a recitation of the end result of the active agent after it has already been administered to the patient. Because the same agent is being administered for the same disease to the same host as presently claimed, any function that the active agent may have after administration is considered to be the necessary end result of the treatment. Thus, absent any factual evidence to the contrary, such a limitation is considered met by the disclosure of Duncan.

Conclusion

Rejection of claims 33-37 is deemed proper.

Claims 1-32 and 38-44 are **withdrawn** pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (8:30 AM-5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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February 17, 2006

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